Guidance for Industry

Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2001
Procedural

Guidance for Industry

Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch (HFD-210)
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573

(Internet) http://www.fda.gov/cder/guidance/index/htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2001
Procedural

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 1

III. DISTRIBUTION PHASE-DOWN 3

IV. BASIS FOR ENFORCEMENT ACTION 4

V. NEW APPLICATIONS 4

A. Patent Certification 4

B. User Fees 5

C. Pediatric Studies 5

D. Therapeutic Equivalence Ratings for Levothyroxine Sodium Products 5

E. Manufacturing Issues 5

1. Stability Data 5

2. Overages 6

3. Dissolution Method 6

Guidance for Industry[1]

Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance discusses how FDA plans to exercise its enforcement discretion after August 14, 2001, with regard to levothyroxine sodium products that are marketed without approved applications. This guidance also answers certain frequently asked questions concerning the submission of applications for levothyroxine sodium products. It replaces the previously issued guidance *Levothyroxine Sodium, Questions and Answers* (February 2001).

II. BACKGROUND

On August 14, 1997, FDA announced in the *Federal Register* (62 FR 43535) that orally administered levothyroxine sodium drug products are new drugs. The notice stated that by August 14, 2000, manufacturers who wish to continue to market these products must obtain approved applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR part 314. The notice stated that after August 14, 2000, any orally administered drug product containing levothyroxine sodium that is introduced or delivered for introduction into interstate commerce without an approved

[1] This guidance has been prepared by the Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

application will be subject to regulatory action, unless found by FDA to be not subject to the new drug requirements of the Act under a citizen petition submitted for that product.[2] On April 26, 2000, FDA issued a second *Federal Register* notice (65 FR 24488) extending the deadline for obtaining approved applications until August 14, 2001.

The Agency permitted orally administered levothyroxine sodium products to remain on the market during this period of time without approved new drug applications to give manufacturers time to conduct the required studies, prepare applications, and have them approved because FDA found that levothyroxine sodium products are medically necessary. FDA stated in the 1997 notice that levothyroxine sodium products are used to treat hypothyroidism, and no alternative drug is relied on by the medical community as an adequate substitute. FDA also stated that the permission to remain on the market without an approved application applies only to products marketed on or before the date of the August 14, 1997, notice.

As of June 2001, two orally administered levothyroxine sodium products have been approved by FDA. Unithroid, manufactured by Jerome Stevens Pharmaceuticals, was approved on August 21, 2000. Levoxyl, manufactured by Jones Pharma, was approved on May 25, 2001. These approved products have been evaluated by FDA and found to be safe and effective for their intended uses. FDA has not evaluated the safety and effectiveness of unapproved marketed products, but it has determined that no currently marketed unapproved orally administered levothyroxine sodium product is generally recognized as safe and effective (August 14, 1997 *Federal Register* notice, p. 43538).

Notwithstanding the fact that there are now two approved applications for orally administered levothyroxine sodium, FDA has determined that it will take time for the millions of patients taking unapproved products to switch to approved products, and for manufacturers of approved products to scale up their production and to introduce this increased production into the distribution chain.

To the maximum extent possible, FDA seeks to allow the initial evaluation by a physician regarding the switch to an approved product to occur within the context of a patient's normal visits.[3] Many patients are only seen every 6-12 months, and FDA would like to minimize the number of visits required outside of these routine appointments. In addition, it may take several months for other patients to make an initial appointment to be evaluated.

Therefore, in order for manufacturers of approved products to scale up their production and for patients and health care providers to make a reasonable transition from unapproved to approved products, FDA has decided to continue to exercise its enforcement discretion by establishing a gradual phase-out of unapproved products as described below.

---

[2] FDA has not found any orally administered levothyroxine sodium drug products to be generally recognized as safe and effective in response to a citizen petition.

[3] In addition, several physician office visits over as much as 6 months to one year may be necessary to adjust optimally the dose of a new product.

III. DISTRIBUTION PHASE-DOWN

Manufacturers of orally administered levothyroxine sodium products with applications pending at the FDA on August 14, 2001, should reduce the distribution of these products as follows:

- By November 1, 2001, average monthly distribution in the preceding 2 ½ months should have been reduced to 95% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By February 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 90% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By May 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 80% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By August 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 60% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By November 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 45% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By February 1, 2003, average monthly distribution in the preceding 3 months should have been reduced to 30% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By May 1, 2003, average monthly distribution in the preceding 3 months should have been reduced to 15% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By August 14, 2003, all distribution should cease.

Starting November 1, 2001, an applicant should submit quarterly amendments to its pending application certifying that the applicant has reduced average monthly distribution in accordance with the above phase-down schedule. Each certification should include a clear statement of the total amount of each strength of the product actually distributed in that quarter. The first certification should include clear and complete information on how the average monthly distribution over the 6 months preceding August 1, 2001, was determined. If FDA approves the application before August 14, 2003, the product may be distributed after the date of approval without regard to the phase-down schedule.

Manufacturers of levothyroxine sodium products who do not have an application approved or pending before the Agency on August 14, 2001, should cease distribution of their products immediately on August 14, 2001, or on any date thereafter that they do not have an application approved or pending with the Agency (e.g., if the application is withdrawn). If they do not cease distribution, they will be subject to regulatory action.

IV. BASIS FOR ENFORCEMENT ACTION

Orally administered levothyroxine sodium drug products are new drugs. Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) states: "No person may introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." A manufacturer who introduces or delivers for introduction into interstate commerce an unapproved drug product is subject to injunction, prosecution, or seizure as authorized by sections 302, 303, and 304 of the Act (21 U.S.C. 332, 333, 334). Violation of an injunction could result in a contempt proceeding or such other penalties as a court may order (e.g., fines). However, FDA does not intend to take action for marketing without an approved application against a manufacturer of a levothyroxine sodium drug product who complies with the plan for phased reduction of distribution described in section III.

V. NEW APPLICATIONS

Until August 14, 2001, FDA will continue to accept 505(b)(2) applications for levothyroxine sodium products. After that time, FDA will exercise its authority under section 314.101(d)(9) to refuse to file a 505(b)(2) application submitted for a levothyroxine sodium product that is eligible for approval under section 505(j).[4] A manufacturer who wishes to submit an application for such a product after August 14, 2001, should submit an abbreviated new drug application (ANDA). FDA has designated Unithroid as the reference listed drug to which ANDAs should refer. However, the Agency would accept a petition to designate a second reference listed drug.

A. Patent Certification

All 505(b)(2) and 505 (j) applications are subject to the patent certification requirements at 21 CFR 314.50(i) and 314.94(a)(12). Now that NDAs have been approved and there is a listed drug, applications that have been submitted or filed, but not yet approved, may need to be amended to include a patent certification for any patent listed for the listed drug. If there are no patents listed for the listed drug (there were none at the time of the

[4] An applicant should submit a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data. However, after August 14, 2001, section 505(b)(2) applications should not be submitted for duplicates of approved products that are eligible for approval under 505(j) (see 21 CFR 314.101(d)(9)).

issuance of this guidance), the applicant may only need to submit a statement, as described at 314.50(i)(1)(ii) and 314.94(a)(12)(ii), that there are no relevant patents.

B. User Fees

A 505(b)(2) application seeking approval for levothyroxine sodium as single agent therapy for thyroid-related disorders will not be assessed a user fee. A 505(b)(2) application for levothyroxine sodium seeking approval of an indication for a use different from that previously approved will be assessed a fee. An ANDA will not be assessed a user fee. For further information on user fees, see http://www.fda.gov/oc/pdufa.

C. Pediatric Studies

As of April 1, 1999, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment, unless such studies are waived or deferred (63 FR 66632; December 2, 1998, *the pediatric rule*). Applications for levothyroxine sodium are subject to the pediatric rule. Applicants should discuss with the Division of Metabolic and Endocrine Drug Products, or the Office of Generic Drugs if the application is submitted under 505(j), whether a pediatric assessment is needed for the levothyroxine sodium product proposed in the application, or whether a waiver would be appropriate.

D. Therapeutic Equivalence Ratings for Levothyroxine Sodium Products

At the time of the issuance of this guidance, there were two approved 505(b)(2) applications for levothyroxine sodium tablets. These two, and any 505(b)(2) applications approved in the future, will be listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) as BX-rated drug products for which the data are insufficient to determine therapeutic equivalence. To obtain a therapeutic equivalence rating other than BX for levothyroxine sodium tablets, an applicant should submit data comparing its product to a listed drug. If upon review of the data, the two products are determined by FDA to be bioequivalent, they would be AB-rated to each other in the Orange Book.

E. Manufacturing Issues

1. Stability Data

FDA recommends that 6 months' long-term stability data and 3 months' accelerated stability data be included when the application is submitted. Primary stability data should be generated according to guidance developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[5] Additional stability data may be submitted as an amendment during the review process, and an expiration date will be determined based on FDA review of the data submitted.

[5] *Q1A Stability Testing of New Drug Substances and Products* (September 1994).

2. Overages

The finished product should be formulated to be released at 100% of the labeled claim. Similarly, the primary stability studies submitted in support of the application should be performed with lots released for stability testing at 100% of the labeled claim. The proposed shelf life should not depend on the existence of a stability overage.

3. Dissolution Method

505(b)(2) applicants should consult with the Division of Metabolic and Endocrine Drug concerning dissolution testing. 505(j) applicants should consult with the Office of Generic Drugs.